

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

CONTAG et al.

Serial No.: 08/844,336

Filing Date: April 18, 1997

Title: BIODETECTORS TARGETED TO
SPECIFIC LIGANDS

Examiner: R. Zeman

Group Art Unit: 1645

Confirmation No.: 7227

Customer No.: 20855

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal Brief is filed in response to the Final Office Action dated January 17, 2007 and the Advisory Action dated April 16, 2007. A Notice of Appeal was received in the USPTO on May 17, 2007. A request for two-month extension and appropriate fee are submitted herewith, making an Appeal Brief filed on or before September 17, 2007 timely filed.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST.....	3
II. RELATED APPEALS AND INTERFERENCES.....	3
III. STATUS OF CLAIMS	3
IV. STATUS OF AMENDMENTS.....	3
V. SUMMARY OF CLAIMED SUBJECT MATTER	3
VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL	5
VII. ARGUMENTS	5
CLAIMS APPENDIX.....	13
EVIDENCE APPENDIX.....	15
RELATED PROCEEDINGS APPENDIX.....	16

I. REAL PARTY IN INTEREST

The real party in interest is Xenogen Corporation, assignee of the instant application, as recorded in the USPTO at Reel 9497/Frame 0636 on October 6, 1998.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1, 3-9, 21, 22, 25, 26, and 27 are pending. Claims 1, 3-9, 21, 22, and 27 were finally rejected in the Final Office Action dated January 17, 2007. Claims 25 and 26 were objected to for being dependent on a rejected claim. Claims 2, 10-20, and 23-24 were canceled. Thus, claims 1, 3-9, 21, 22, and 27 are under appeal as shown in the Claims Appendix attached hereto.

IV. STATUS OF AMENDMENTS

No amendments have been made subsequent to the mailing of the Final Office Action on January 17, 2007.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 recites a biodetector for the detection of a selected substance (specification, *e.g.*, at page 6, lines 18-19 and page 8, lines 13-20). The claimed biodetector comprises: (a) a transmembrane fusion protein comprising an extracellular ligand-specific moiety and an intracellular enzymatic signal transforming domain, wherein the extracellular ligand-specific moiety comprises an antibody that binds the selected substance, which binding activates the intracellular enzymatic signal transforming domain (specification, *e.g.*, at page 6 lines 20-22; page 14, lines 23-26; and page 15, lines 8-27); (b) a transducer that has an inactive form and an active form which are distinct from each other, wherein the activated intracellular enzymatic signal transforming domain converts the inactive form of the transducer into the active form of

the transducer (specification, *e.g.*, at page 6, lines 22-23; page 11, lines 9-12; page 14, lines 23-29; page 15, lines 24-27; and page 16, lines 11-22); and (c) a responsive element comprising a transcription activation element, wherein the responsive element is activated by the active form of the transducer, resulting in a detectable signal (specification, *e.g.*, at page 6, lines 23-24; page 9, lines 26-29; page 10, lines 1-7; page 11, lines 12-15; and page 16, lines 16-22).

Claim 3 depends from claim 1 and specifies that the responsive element further comprises a nucleic acid encoding one or a plurality of gene products that produce the detectable signal, and wherein the nucleic acid is operatively linked to the transcription activation element (specification, *e.g.*, at page 14, lines 6-9 and 26-29; page 16, lines 18-20).

Claim 4 depends from claim 3 and further specifies that the detectable signal of the biodetector is light (specification, *e.g.*, at page 9, lines 22-23; page 10, lines 6-16; page 19, line 10 through page 22, line 21).

Claim 5 depends from claim 3 and further specifies that the gene product is detectable by bioluminescence, colorimetric reactions, or fluorescence (specification, *e.g.*, at page 16, lines 24-25).

Claim 6 depends from claim 3 and further specifies that the nucleic acid comprises a luciferase operon (specification, *e.g.*, at page 11, lines 15-18; page 17, line 18 through page 19, line 5; Figure 4; and Example 1).

Claim 7 depends from claim 1 and further specifies that the intracellular enzymatic signal transforming domain is a membrane signal transducer (specification, *e.g.*, at page 11, lines 2-9).

Claim 8 depends from claim 7 and further specifies that the membrane signal transducer is selected from the group consisting of bacterial two-component regulatory systems, eukaryotic receptor-mediated signal transducers, and prokaryotic receptor-mediate signal transducers (specification, *e.g.*, at page 10, lines 2-4; and Examples 1-3).

Claim 9 depends from claim 6 and further specifies that the selected substance is selected from the group consisting of microorganism, virus, retrovirus, protein, sugar and ion (specification, *e.g.*, at page 9, lines 1-4; page 15, lines 1-3; and page 23, lines 2-29).

Claim 21 depends from claim 1 and further specifies that the intracellular enzymatic signal transforming domain is derived from PhoQ (specification, *e.g.*, at page 15, lines 29-30).

Claim 22 depends from claim 1 and recites a genetically engineered bacterial cell comprising a biodetector according to claim 1 (specification, *e.g.*, at page 8, lines 27-29; page 11, lines 4-18).

Claim 27 depends from claim 5 and further specifies that the gene product is detectable by means of bioluminescence (specification, *e.g.*, at page 16, lines 24-25; page 17, line 18 through page 19, line 5).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1, 3-9, 21, 22, and 27, directed to biodetectors and engineered bacterial cells comprising biodetectors, are obvious under 35 U.S.C. §103 over U.S. Patent No. 5,521,066 (hereinafter "Menzel") in view of U.S. Patent No. 5,348,867 (hereinafter "Georgiou").

VII. ARGUMENTS

The rejection of claims 1, 3-9, 21, 22, and 27 under 35 U.S.C. § 103 is improper, as the claimed subject matter is not obvious in view of the references of Menzel and Georgiou.

Claims 1, 3-9, 21, 22, and 27 stand rejected under 35 U.S.C. § 103(a), based on the allegation that the claims are unpatentable over Menzel et al. (U.S. Patent No. 5,521,066; hereinafter "Menzel") in view of Georgiou et al. (U.S. Patent No. 5,348,867; hereinafter Georgiou). Menzel is cited for disclosing a transmembrane fusion protein comprising a ligand binding domain, a cytoplasmic toxR DNA binding region, a hydrophobic toxR transmembrane region and a reporter gene operably linked to a ctx

operon. (Office Action of July 21, 2006, page 5). Menzel is further alleged to disclose that binding a ligand to the ligand binding domain induces a conformational change in the cytoplasmic domain, which in turn induces binding to the promoter region of the reporter gene. The rejection alleges in particular that, although Menzel does not explicitly disclose the use of antibodies on bacterial surfaces, it would have been obvious to use Georgiou's heterologous scFV antibodies in Menzel's fusion proteins (see Advisory Action, pages 5-6).

Appellants submit the Examiner has improperly rejected the claims, as the combination of references does not teach all the elements of the claims on appeal and actually teaches away from the claimed biodetectors.

The recent decision by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007) reaffirmed the viability of the four factual inquiries underlying an obviousness analysis provided in *Graham v. John Deere*, 148 USPQ 459, 467 (U.S. 1966). These factors include: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary considerations. Moreover, the Supreme Court in *KSR* recognized that the "teaching, suggestion, or motivation" analysis provides a helpful insight in determining whether the claimed subject matter is obvious. This analysis is provided in MPEP 2142. In particular, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Both the teaching or suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art, not in applicant's disclosure. See, e.g., *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Based on the foregoing, Appellants respectfully submit the Office has failed to establish a *prima facie* case of obviousness. The Office has failed to provide evidence

that the claimed subject matter is a “predictable use of prior art elements according to their established functions.” *KSR*, page 13. In fact, the evidence is to the contrary. The cited art fails to teach or suggest all the elements of the claimed biodetectors.

To briefly reiterate, claims 1, 3-9, 21, and 27 are directed to biodetectors comprising three elements: (1) a transmembrane fusion protein having an extracellular antibody domain and an intracellular enzymatic signal transforming domain which is activated upon binding of a selected substance to the antibody; (2) a transducer which is activated by the activated intracellular enzymatic signal domain of the transmembrane fusion protein; and (3) a transcription activation element that is activated by the active form of the transducer, to give a detectable signal. Claim 22 is directed to a genetically engineered bacterial cell comprising such a biodetector.

A. The combination of references does not teach or suggest all the elements of the claims and teaches away from the claimed subject matter.

1. The toxR-ctx system of Menzel only detects dimerization

Menzel pertains to a toxR-ctx system for detection of dimerization of a toxR fusion protein. ToxR is a transmembrane protein containing a DNA binding domain at its N-terminus. Dimerization of toxR modulates the ability of the N-terminus of toxR to bind to the ctx promoter and initiate transcription. In the toxR-ctx system, dimerization of a toxR fusion protein is detected by a reporter gene linked to the ctx operon. Appellants emphasize that dimerization is what is detected by Menzel’s system. See Menzel, *e.g.*, at col. 1, lines 33-36; col. 2, lines 3-6; and col. 4, lines 15-17. See also claim 5, which recites a process for detecting dimer formation of the toxR fusion protein. In contrast, the biodetector of the appealed claims detects binding of a substance (dimer or otherwise) by its binding to an extracellular antibody domain, which triggers a cascade resulting in a detectable signal.

2. The toxR-ctx system of Menzel has no intracellular enzymatic signal domain

Furthermore, unlike Menzel, the claimed biodefectors uses activation of an intracellular enzymatic signal domain of a transmembrane fusion protein for transducing a signal to a transcription activation element. Binding of a ligand to the biosensor activates the enzymatic activity of this intracellular domain and transmits a signal to the transducer, which in turn, is converted to an active form that initiates transcription of a reporter gene (see specification, *e.g.*, at page 11, lines 9-31; page 14, lines 21-29). The intracellular enzymatic signal domain can comprise an enzyme or an active domain of an enzyme that has, for example, a protein modifying function, such as phosphorylation, dephosphorylation, methylation, acetylation, or protease activity (see specification, *e.g.*, at page 15, lines 24-28).

Because this component of the claimed biosensor is entirely lacking in the system described by Menzel (which relies simply on dimerization of toxR and no secondary mediator), Menzel does not teach or suggest all the elements of the claims.

3. The toxR-ctx system of Menzel has no extracellular antibody domain

Nor does Menzel describe or suggest using an extracellular antibody domain for detecting substances through ligand binding. Antibodies that bind a particular substance can be readily generated by one of ordinary skill in the art by eliciting an immune response to the substance or by production recombinantly. Thus, an advantage of the present system is that a wide variety of selected substances can be detected with biosensors as claimed that use antibody domains for ligand binding (see specification, *e.g.*, at page 12, lines 4-9; and page 15, lines 1-4). In contrast, the system of Menzel only detects substances that are capable of modulating dimerization of a toxR fusion protein.

With regard to the Examiner's contention that certain antibody classes (*e.g.*, IgA) can form dimers that could be used in Menzel's system (see Advisory Action, page 4), Appellants respectfully disagree. Natural immunoglobulins generally have a tetrameric,

not a dimeric structure, and are made up of two light chains and two heavy chains. Some classes of immunoglobulins, such as IgA, can form polymers of this basic tetrameric structure. Appellants emphasize that the association of heavy and light chains in antibodies is not dependent on ligand binding and occurs in the absence of a ligand. Furthermore, Menzel does not simply detect a conformational change in toxR, as the Examiner asserts (see Advisory Action, page 5), but rather, the dimerization of toxR, which is required for toxR to associate with the ctx operon to activate expression of a reporter gene (see Menzel, *e.g.*, at col. 1, lines 33-36; col. 2, lines 3-6; and col. 4, lines 15-17).

Therefore, Menzel teaches away from any system in which dimerization itself is not modulated by the substance that is to be detected. In contrast, the instant claims detect ligand binding to an antibody domain, not dimerization of an antibody.

4. Georgiou fails to fill the gaps of Menzel

The secondary reference of Georgiou fails to make up for the deficiencies of Menzel. Georgiou pertains to methods for expressing proteins on the surface of bacterial cells by using a tripartite chimeric gene having a membrane targeting sequence, a sequence encoding a transmembrane segment, and a sequence encoding a selected protein of interest. Although Georgiou describes expression of single-chain antibodies using this method, as the Examiner asserts (Advisory Action, page 5), Georgiou fails to describe or suggest any method for detecting a selected substance bound to an antibody on the surface of a bacterial cell. In particular, Georgiou fails to describe or suggest any intracellular enzymatic signal domain for transducing a signal to a transcription activation element. Thus, neither Georgiou nor Menzel, alone or in combination, describe or suggest a recited element of the claims.

B. There is no motivation to combine the cited references as set forth in the rejection.

As noted above, the Supreme Court has determined that the “teaching, suggestion, motivation” test provides valuable insight into an obviousness inquiry. In this case on appeal, the combination of Menzel and Georgiou fails to teach or suggest all the components of the claimed biosensors. Moreover, the references fail to provide any motivation for producing a biosensor that includes, in particular, an extracellular antibody domain and an intracellular enzymatic signal domain for transmitting a signal via a transducer to a transcription activation element for detection of a selected substance.

Georgiou describes expression of single-chain antibodies on bacterial cells for use as whole cell adsorbents (col. 6, lines 29-32). No motivation can be found anywhere in Georgiou for using surface expression of antibodies to create a biosensor, as claimed. Appellants again emphasize that the system of Menzel detects dimerization, not ligand binding per se. Therefore, Menzel teaches away from any system that does not necessarily involve dimerization of a fusion protein. The single-chain antibodies, taught by Georgiou, contain a polypeptide linker, which joins immunoglobulin light and heavy chain variable domains to form a functional antigen-binding pocket. Binding of antigen to such a single-chain antibody is, therefore, not expected to promote dimerization of a fusion protein comprising such a single-chain antibody. Thus, the single-chain antibodies taught by Georgiou would not work in the system taught by Menzel.

As set forth in M.P.E.P. 2143.01 (V), “[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).” Therefore, no motivation can be found for combining the teachings of Menzel and Georgiou.

Nonetheless, the Examiner has maintained that “it would have been obvious to one of skill in the art to use the heterologous scFv disclosed by Georgiou et al. in order to take advantage of the increase in specificity, diversity and ease of production associated with the resulting fusion protein (biodetector)” (Advisory Action, page 6). However, there is nothing in the prior art as a whole to suggest the desirability of making this combination. The Examiner is using impermissible hindsight reasoning to reconstruct the

claimed subject matter by combining references where clearly the advantages of combining the components were unrecognized. The claimed biodetectors provide an improvement over the existing art in providing a biosensor with the significant advantage of having the capability of detecting a wide variety of selected substances. In contrast, the system of Menzel only detects substances capable of modulating dimerization of a toxR fusion protein. Georgiou fails to describe or suggest any type of biosensor.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000). Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show “reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed.” *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

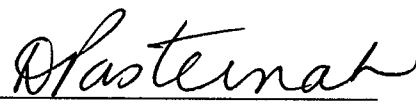
The references of Menzel and Georgiou do not teach or suggest all the elements of the pending claims, including the particularly claimed biodetectors (claims 1, 3-9, 21, and 27) and the genetically engineered bacterial cells comprising the biodetectors (claim 22). For all of the aforementioned reasons, the rejection of claims 1, 3-9, 21, 22, and 27 under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are non-obvious and patentable. Accordingly, Appellants request that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

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CLAIMS APPENDIX

The claims on appeal are as follows:

1. A biodetector for the detection of a selected substance comprising:
 - (a) a transmembrane fusion protein comprising an extracellular ligand-specific moiety and an intracellular enzymatic signal transforming domain, wherein said extracellular ligand-specific moiety comprises an antibody and wherein said antibody binds said selected substance, which binding activates said intracellular enzymatic signal transforming domain;
 - (b) a transducer, wherein said transducer has an inactive form and an active form which are distinct from each other, and said activated intracellular enzymatic signal transforming domain converts said inactive form of said transducer into said active form of said transducer;
 - (c) a responsive element comprising a transcription activation element, wherein said responsive element is activated by said active form of said transducer, resulting in a detectable signal.
3. The biodetector of claim 1, wherein said responsive element further comprises a nucleic acid encoding one or a plurality of gene products, which gene product or gene products produce said detectable signal, and wherein said nucleic acid is operatively linked to said transcription activation element.
4. The biodetector of claim 3 wherein said detectable signal is light.
5. The biodetector or claim 3, wherein said gene product is detectable by means selected from the group consisting of bioluminescence, colorimetric reactions or fluorescence.

6. The biodeceptor of claim 3, wherein said nucleic acid comprises a luciferase operon.
7. The biodeceptor of claim 1, wherein said intracellular enzymatic signal transforming domain is a membrane signal transducer.
8. The biodeceptor of claim 7, wherein the membrane signal transducer is selected from the group consisting of bacterial two-component regulatory systems, eukaryotic receptor-mediated signal transducers, and prokaryotic receptor-mediate signal transducers.
9. The biodeceptor of claim 6, wherein said selected substance is selected from the group consisting of microorganism, virus, retrovirus, protein, sugar and ion.
21. The biodeceptor of claim 1, wherein said intracellular enzymatic signal transforming domain is derived from PhoQ.
22. A genetically engineered bacterial cell comprising a biodeceptor according to claim 1.
27. The biodeceptor of claim 5, wherein said gene product is detectable by means of bioluminescence.

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EVIDENCE APPENDIX

No documents are submitted in the Evidence Appendix.

RELATED PROCEEDINGS APPENDIX

As noted above, Appellants are not aware of any related appeals or interferences. Accordingly, no documents are submitted with this Appendix.